IV. General Approach to Treatment—Goals and Thresholds

The basic principle that guides cholesterol-lowering intervention is that the intensity of treatment is directly related to the degree of risk for CHD events. Both short-term (10-year) risk and long-term risk must be considered for treatment decisions. Persons with existing CHD (or a CHD risk equivalent) are at the highest risk; for this reason, they have the lowest goal level for LDL cholesterol and receive the most intensive treatment. For persons without CHD, classification and treatment goals are based on the category of risk, of which there are two—multiple (2+) risk factors other than LDL, and 0–1 risk factor. Persons with 2+ risk factors have an LDL goal that is not quite as low as that for persons with CHD (or CHD risk equivalents). ATP III differs from ATP II in that it distinguishes three subcategories of risk among persons with multiple (2+) risk factors: 10-year risk for hard CHD >20 percent, 10–20 percent, and <10 percent. Among the group with multiple risk factors, those at highest risk receive the most intensive LDL-lowering therapy, and those with the lowest risk receive the least intensive therapy. For persons with 0–1 risk factor, LDL goal levels are not as low as for persons with multiple risk factors, and intensive LDL-lowering therapy is not required unless LDL cholesterol levels are very high.

1. Therapeutic goals for LDL cholesterol

ATP III recommends that LDL cholesterol be the primary target of therapy. The LDL cholesterol goals for each risk category are shown in Table IV.1–1.

Table IV.1–1. LDL Cholesterol Goals for Three Risk Levels

Risk Level	LDL-C Goal
CHD and CHD Risk Equivalent	<100 mg/dL
Multiple (2+) Risk Factors	<130 mg/dL*
0–1 Risk Factor	<160 mg/dL

* LDL-C goal for multiple-risk-factor persons with 10-year risk >20 percent = <100 mg/dL.

Persons with CHD or CHD risk equivalent have an LDL cholesterol goal of <100 mg/dL. Those with multiple risk factors have an LDL cholesterol goal of <130 mg/dL; an exception is the patient with a CHD risk equivalent (>20 percent per 10 years) who has an LDL cholesterol goal <100 mg/dL. Finally, those with 0–1 risk factor have a goal LDL cholesterol of <160 mg/dL. These goals are set to maximize reduction in both short-term and long-term risk.

For persons whose LDL cholesterol levels are above the goal for the category, the goal of therapy is achieved through the judicious use of dietary and drug therapies. Dietary therapy in clinical management is designated the Therapeutic Lifestyle Changes (TLC) Diet. This diet includes the following: (a) reduced intakes of saturated fats and cholesterol, (b) therapeutic dietary options to enhance LDL lowering (plant stanols/sterols and increased viscous fiber), (c) weight control, and (d) increased physical activity (see Section V). The drugs available for LDL-cholesterol-lowering are presented in Section VI.

ATP III recommends a two-step approach to cholesterol management. Priority goes to attaining the goal for LDL cholesterol; thereafter emphasis shifts to management of the metabolic syndrome and other lipid risk factors. Figure IV.1–1 shows the physician's responsibility at the first visit. Once the lipoprotein analysis is evaluated, risk factor counting and, if necessary, 10-year risk assessment are carried out to determine risk status. The patient is then started on dietary therapy or discharged with instructions for appropriate life-habit modifications. If the patient has CHD or a CHD risk equivalent, LDL-lowering drug therapy can be started simultaneously with dietary therapy if the LDL level warrants.

After an appropriate trial of dietary therapy to reduce LDL cholesterol (~ 3 months), two additional therapeutic decisions may be required. First, if the LDL cholesterol goal has not been achieved, consideration may be given to initiating drug therapy. Second, if the metabolic syndrome is present, additional lifestyle changes (i.e., weight reduction and increased physical activity) will be needed. Later, if lifestyle therapies do not alleviate the metabolic syndrome, drug therapy for treatment of the metabolic risk factors may be required.

2. Management of LDL Cholesterol

The following summarizes the ATP III approach to management of persons in the three categories of risk.

a. CHD and CHD risk equivalents

For persons with CHD and CHD risk equivalents, the type and intensity of LDL-lowering therapy are adjusted according to baseline LDL cholesterol level, i.e., whether ≥130 mg/dL, 100–129 mg/dL, or <100 mg/dL (Table IV.2–1 and Figure IV.2–1). Each subcategory of LDL cholesterol is discussed below.

Table IV.2–1. Therapeutic Approaches to LDL Cholesterol Lowering in Persons with CHD or CHD Risk Equivalents

Subcategory of LDL Cholesterol Level	LDL Cholesterol Goal	Level at Which to Initiate Dietary Therapy (TLC)	Level at Which to Initiate LDL-Lowering Drugs
≥130 mg/dL	<100 mg/dL	≥100 mg/dL	Start drug therapy simultaneously with dietary therapy
100–129 mg/dL	<100 mg/dL	≥100 mg/dL	Consider drug options*
<100 mg/dL	<100 mg/dL	TLC & emphasize weight control and physical activity	LDL-lowering drugs not required

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify other lipoprotein fractions, e.g., nicotinic acid and fibrate. Clinical judgment also may call for withholding drug therapy in this subcategory.

1) Baseline LDL cholesterol ≥130 mg/dL

Persons with LDL cholesterol ≥130 mg/dL generally will require an LDL-lowering drug to achieve LDL cholesterol <100 mg/dL. Therefore, a cholesterol-lowering drug should be initiated simultaneously with TLC and maximal control of other risk factors. If the LDL cholesterol falls to the range of 100–129 mg/dL on cholesterol-lowering therapy, several options are available depending on circumstances.

- LDL lowering can be intensified with dietary therapy to achieve an LDL cholesterol level <100 mg/dL.
- LDL lowering can be intensified with drug therapy to achieve an LDL cholesterol level <100 mg/dL.
- If the on-treatment LDL cholesterol level is near the goal of therapy, the physician can maintain the current LDL-lowering therapy unchanged.
- If the metabolic syndrome is present, dietary therapy is intensified by increased efforts to reduce excess weight and increase physical activity.
- If the patient has elevated triglycerides or low HDL, a different lipid-lowering drug can be considered (e.g., nicotinic acid or fibric acid) for combination therapy with an LDL-lowering drug (see Section VI).

2) Baseline LDL cholesterol 100–129 mg/dL

When baseline LDL cholesterol is 100–129 mg/dL, several therapeutic options likewise are available. All approaches include TLC as initial therapy. Depending on circumstances, the following options are available:

- Inclusion of therapeutic dietary options (e.g., plant stanol/sterols and increased viscous fiber) can help to achieve the LDL goal.
- If LDL cholesterol levels remain appreciably above 100 mg/dL after 3 months of maximal dietary therapy, consideration can be given to adding an LDL-lowering drug.
- If the patient has an elevated triglyceride or low HDL cholesterol level, another lipid-lowering drug can be considered (e.g., nicotinic acid or fibric acid).
- If the LDL cholesterol level falls to near the goal on dietary therapy alone, the physician can choose to forgo use of a lipid-lowering drug for the present.

Because other risk factors may have contributed importantly to development of CHD in persons with low LDL levels, maximal control of nonlipid risk factors is necessary.

3) Baseline LDL cholesterol <100 mg/dL

If baseline LDL cholesterol is below the goal of therapy, further LDL-lowering therapy is not currently recommended. Emphasis should be placed on controlling other risk factors and the metabolic syndrome. The TLC diet should be recommended to the person to help maintain a low LDL.

b. Multiple (2+) risk factors

ATP III differs from ATP II in that it distinguishes three subcategories of risk among persons with multiple risk factors, depending on 10-year risk: >20 percent, 10–20 percent, and <10 percent. Within this category of multiple (2+) risk factors, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each subcategory is shown below in Table IV.2–2.

Table IV.2–2. Management of LDL Cholesterol in Persons with Multiple (2+) Risk Factors

10-Year Risk	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy (After TLC)
>20%	<100 mg/dL	≥100 mg/dL	See CHD and CHD risk equivalent
10–20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
<10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL

The following reviews the approach to each subcategory in more detail.

1) Multiple risk factors, 10-year risk >20 percent

Persons with multiple risk factors and 10-year risk >20 percent have a CHD risk equivalent and are treated as described in the previous section (See Figure IV.2–1).

2) Multiple risk factors, 10-year risk 10–20 percent

The goal for LDL cholesterol in this risk category is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, persons are started on TLC for a 3-month trial of dietary therapy, possibly augmented by options for further LDL lowering (plant stanols/sterols and increased viscous fiber). After 6 weeks and again after three months of dietary therapy, lipoprotein analysis is repeated. If LDL remains ≥130 mg/dL after three months, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal <130 mg/dL. Should the LDL be less than 130 mg/dL on dietary therapy alone, it can be continued without adding drug treatment. If the metabolic syndrome is present, more attention should be given to weight control and increased physical activity. See Figure IV.2–2 for the treatment algorithm for this subcategory.

3) Multiple risk factors, 10-year risk <10 percent

The goal for LDL cholesterol in this risk category likewise is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, persons are started on dietary therapy for reducing LDL cholesterol. Options for enhancing LDL lowering can be employed if needed to achieve the goal of therapy. After three months of dietary therapy, lipoprotein analysis is repeated. If LDL is <160 mg/dL on dietary therapy alone, the dietary therapy should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if LDL cholesterol is

≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol <130 mg/dL. See Figure IV.2–3 for the treatment algorithm for this subcategory.

c. Zero to one risk factor

Most persons with 0–1 risk factor have a 10-year risk <10 percent. Guidelines for this category are given in Table IV.2–3.

Table IV.2–3. Management of LDL Cholesterol in Persons with Zero to One (0–1) Risk Factor

Risk Category	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy (After TLC)
0–1 Risk Factor*	<160 mg/dL	≥160 mg/dL	≥190 mg/dL†

* Most persons with 0–1 risk factor have a 10-year risk for CHD <10 percent

† Drug therapy optional for LDL-C 160–189 mg/dL (after dietary therapy)

The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. When baseline LDL cholesterol is ≥160 mg/dL, persons are started on dietary therapy for three months. After 6 weeks, the LDL response is evaluated and dietary enhancers of LDL lowering (plant stanols/sterols and increased viscous fiber) may be added if necessary to reach the LDL goal. After 3 months, lipoprotein analysis is repeated. If LDL cholesterol is <160 mg/dL, dietary therapy is continued. For LDL cholesterol 160–189 mg/dL, drug therapy is optional depending on clinical judgment. Factors that favor use of drugs in this category include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol).
- Multiple life-habit risk factors and emerging risk factors (if measured).
- 10-year risk approaching 10 percent (if measured).

If LDL cholesterol is ≥190 mg/dL despite dietary therapy in persons with 0–1 risk factor, drug therapy can be considered to achieve the goal of therapy in all adults. For persons with severe elevations of LDL cholesterol (e.g., ≥220 mg/dL), drug therapy can be started together with dietary therapy. Most such patients will have genetic forms of hypercholesterolemia that cannot be adequately treated with dietary therapy alone.

d. Management of LDL cholesterol when risk assessment begins with Framingham scoring (Table IV.2–4)

If clinicians choose to begin risk assessment with Framingham risk scoring, the treatment algorithm is similar to that beginning with risk factor counting. The only difference occurs for persons whose 10-year risk is 10–20 percent and who have 0–1 risk factor; if one begins with

risk factor counting, such persons would not have their 10-year risk calculated. This difference occurs in only 2.6 percent of the U.S. population that has 0–1 risk factor.

Table IV.2–4. Management of LDL Cholesterol in Persons Beginning with 10-year Risk Assessment

10-Year Risk	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy (After TLC)
>20%	<100 mg/dL	≥100 mg/dL	See CHD and CHD risk equivalent
10–20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
<10%:			
Multiple (2+) risk factors	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
0–1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL*

* Drug therapy optional for LDL-C 160–189 mg/dL (after dietary therapy)

e. Recommendations for persons whose LDL cholesterol levels are below goal

For persons whose LDL cholesterol levels are already below goal levels upon encounter, instructions for appropriate changes in life habits, periodic follow-up, and control of other risk factors are required (upper portions of Figures IV.1–1, IV.2–2, IV.2–3, and IV.2–4). For all persons without CHD or CHD risk equivalents whose LDL is below goal, the diet for the general public and a physical activity regimen should be recommended. For those with CHD or CHD risk equivalent, the therapeutic diet (TLC diet, see Section V) should be recommended even if the LDL is below goal. Follow-up lipoprotein analysis should be carried out according to Table IV.2–5.

Table IV.2–5. Schedule for Follow-Up Lipoprotein Analysis for Persons Whose LDL Cholesterol Levels are Below Goal Levels

Risk Level	LDL Goal (mg/dL)	LDL Level Observed (mg/dL)	Repeat Lipoprotein Analysis
CHD or CHD risk equivalents	<100	<100	<1 year
2+ risk factors	<130	<130	≤2 years
0–1 risk factor	<160	130–159	≤2 years
0–1 risk factor	<160	<130	≤5 years

f. LDL-lowering therapy in older persons

For primary prevention in persons ≥65 years of age, clinical judgment plays an increasingly important role in decisions about LDL-lowering therapy. Framingham risk scores are less robust for predicting risk in older individuals, and measurements of subclinical atherosclerosis, when available, can assume increasing importance. Rather than routinely applying the algorithms described for persons with multiple risk factors, physician judgment may rely more heavily on the estimated NNT to achieve a reduction in CHD events for the different risk categories (Table II.7–2). Other factors including concomitant chronic diseases, social circumstances, chronological and functional age, and financial considerations must be taken into account when making decisions about therapy, especially about use of LDL-lowering drugs, in older persons.

3. Management of atherogenic dyslipidemia and the metabolic syndrome

After an adequate trial of dietary therapy for LDL lowering, attention should turn to atherogenic dyslipidemia and the metabolic syndrome. Treatment of these conditions usually begins after an initial 3-month period of dietary therapy to lower LDL cholesterol. Therapy for atherogenic dyslipidemia and metabolic syndrome thus begins after the LDL goal has been achieved with TLC alone or simultaneously with initiation of more intensive LDL-lowering therapy with drugs.

a. Atherogenic dyslipidemia

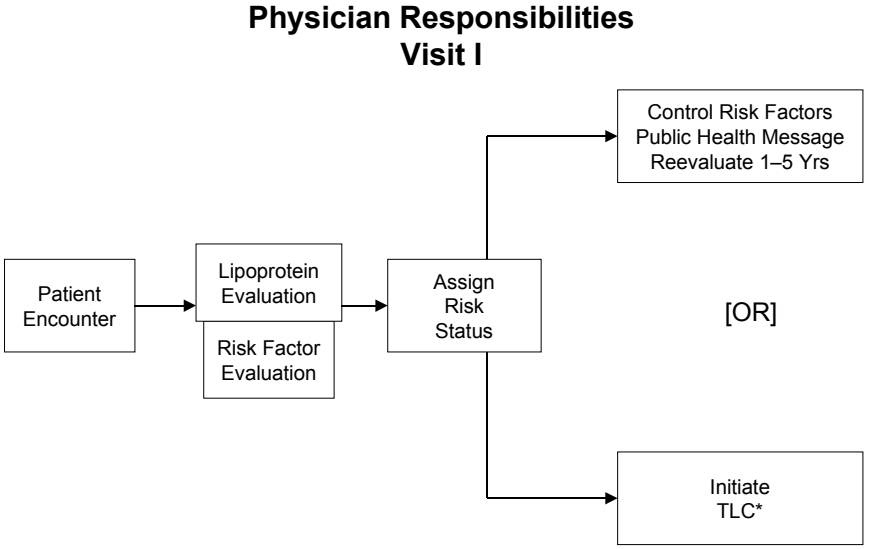
For atherogenic dyslipidemia, treatment strategy focuses on triglycerides. If triglycerides are ≥150 mg/dL and HDL cholesterol is <40 mg/dL, a diagnosis of atherogenic dyslipidemia is made. The patient likely has the metabolic syndrome (see below); if triglycerides are <200 mg/dL, and specific drug therapy to reduce triglyceride-rich lipoproteins (TGRLP) is not indicated. However, if the patient has CHD or CHD risk equivalents, consideration can be given to using a drug to raise HDL cholesterol (fibrate or nicotinic acid), as outlined above under LDL-lowering therapy. On the other hand, if triglycerides are 200–499 mg/dL, non-HDL cholesterol becomes a secondary target of therapy. Goals for non-HDL cholesterol are 30 mg/dL higher than those for LDL cholesterol. First the LDL cholesterol goal is attained, and if non-HDL remains elevated, additional therapy may be required to achieve the non-HDL goal. Alternative approaches for treatment of elevated non-HDL cholesterol that persists after the LDL goal has been achieved are (a) higher doses of statins, or (b) moderate doses of statins + triglyceride-lowering drug (nicotinic acid or fibrate) (see Sections VI and VII). If triglycerides are very high (≥500 mg/dL), attention turns first to prevention of acute pancreatitis, which is more likely to occur when triglycerides are >1000 mg/dL. Triglyceride-lowering drugs (fibrate or nicotinic acid) become first line therapy; although statins can be used to lower LDL cholesterol to reach the LDL goal, in these patients it is often difficult (and unnecessary) to achieve a non-HDL cholesterol goal of only 30 mg/dL higher than for LDL cholesterol.

b. Metabolic syndrome

Beyond treatment of elevated triglycerides, with drugs if necessary, first-line therapy for the metabolic syndrome is change in life habits, especially reducing weight and increasing physical

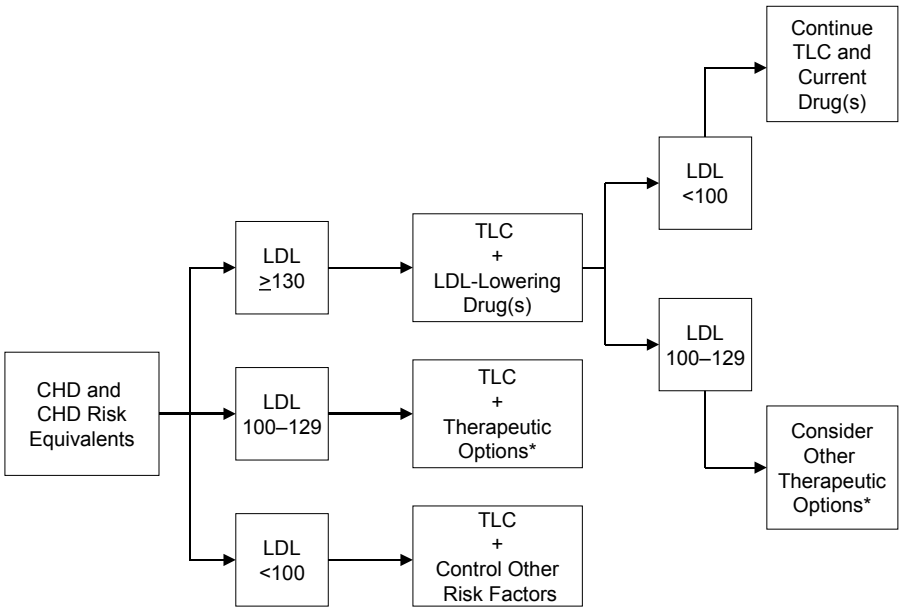
activity. The approach to treatment of the metabolic syndrome with life-habit modification is presented in Section V.

Figure IV.1–1. Physician responsibilities for Visit 1.



* If CHD or CHD risk equivalent are present, drug therapy can be started simultaneously with TLC when LDL-C is ≥130 mg/dL

Figure IV.2–1. Therapeutic approaches to persons with CHD or CHD risk equivalent. The LDL cholesterol goal is <100 mg/dL.



* Therapeutic options include intensifying LDL-lowering dietary or drug therapies, emphasizing weight reduction and increased physical activity, adding drugs to lower triglycerides or raise HDL cholesterol (nicotinic acid or fibrates), and intensifying control of other risk factors.

Figure IV.2–2. Therapeutic approaches to persons with multiple risk factors, 10-year risk 10–20 percent. The LDL cholesterol goal is <130 mg/dL. Drugs can be considered if necessary to attain the LDL cholesterol goal if the LDL cholesterol level is ≥130 mg/dL after a trial of TLC.

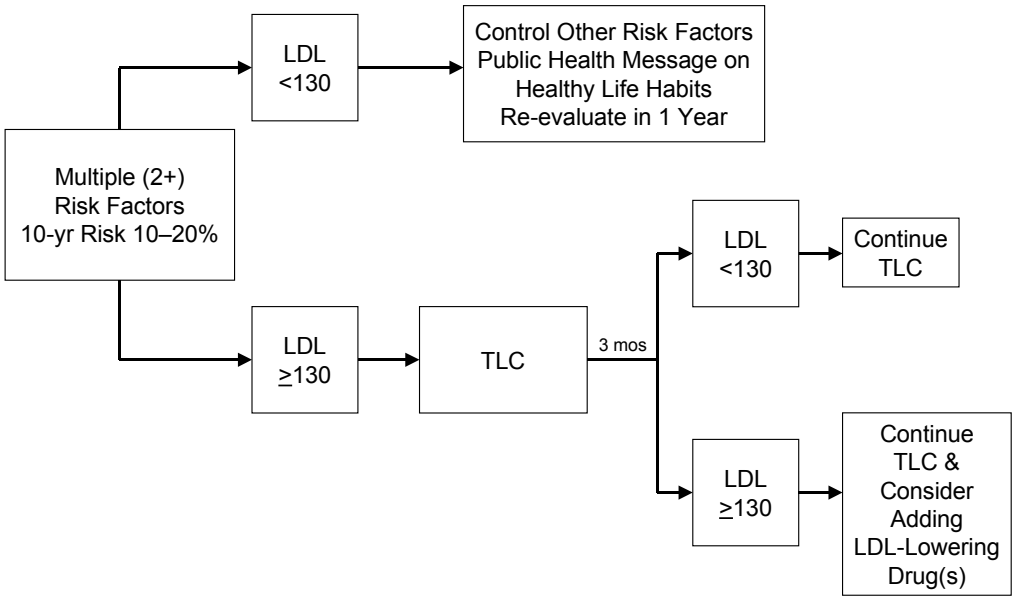


Figure IV.2–3. Therapeutic approaches to the patient with multiple (2+) risk factors, 10-year risk <10 percent. The LDL cholesterol goal is <130 mg/dL. Drug therapy can be considered if LDL cholesterol is ≥160 mg/dL after a trial of TLC.

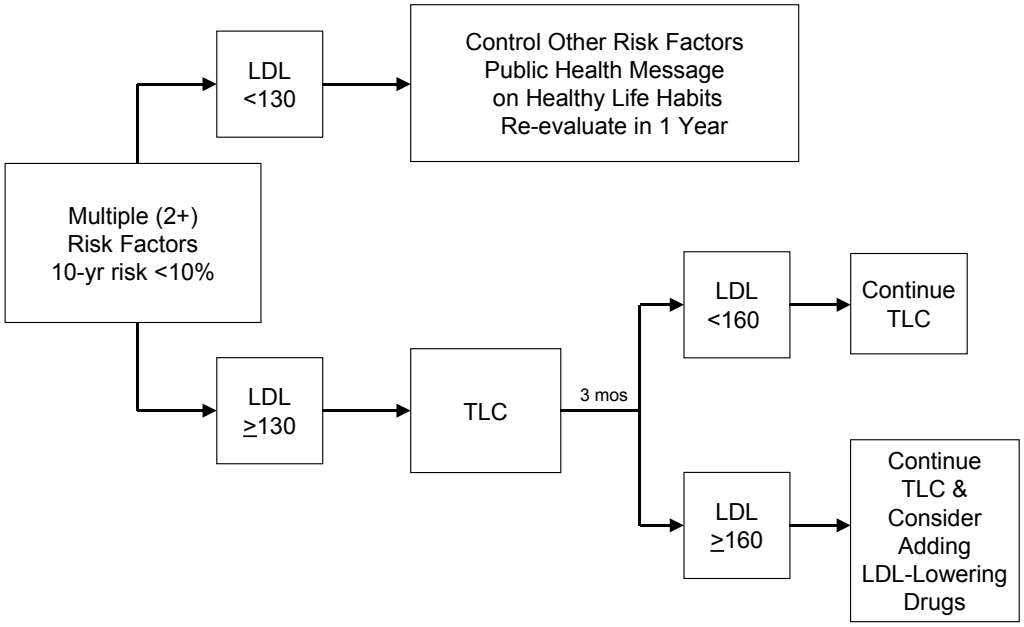
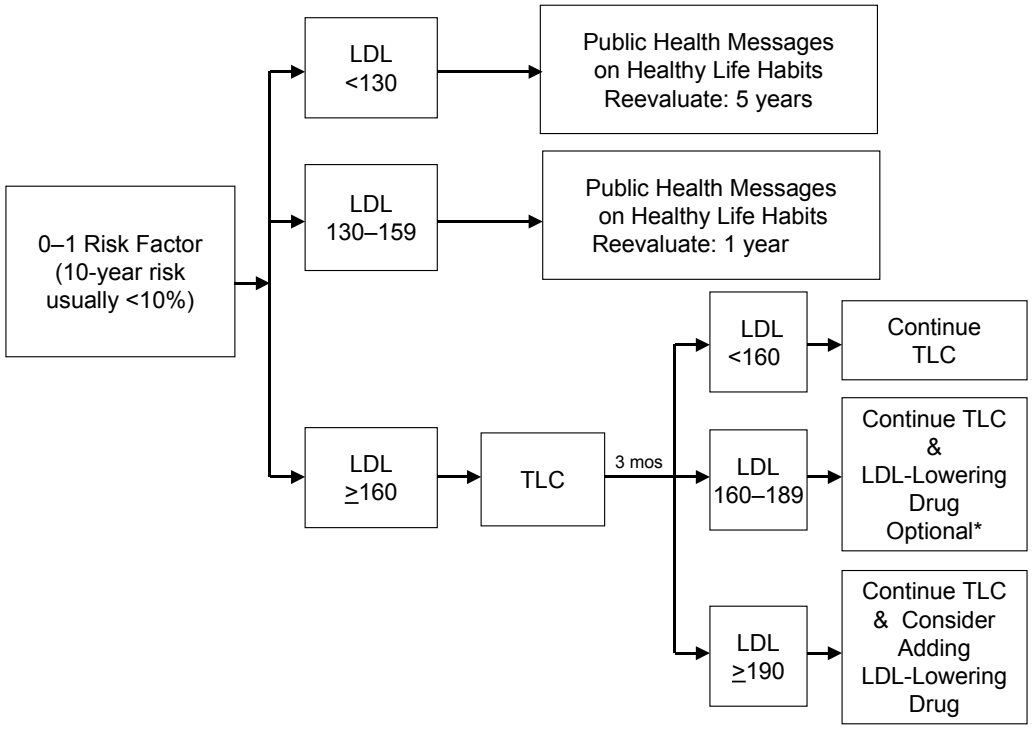


Figure IV.2–4. Therapeutic approaches to persons with 0–1 risk factor. The LDL cholesterol goal is <160 mg/dL. Drug therapy can be considered if the LDL cholesterol level is ≥190 mg/dL after a trial of TLC. If LDL cholesterol is 160–189 mg/dL, drug therapy is optional depending on clinical judgment.



* Factors favoring drug use are a severe single risk factor, a family history of premature CHD, and/or underlying or emerging risk factors in addition to a single major risk factor